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Citation for published version:

Parra, M, Abrahams, S, Logie, RH, Mendez, LG, Lopera, F & Della Sala, S 2010, 'Visual short-term memory binding deficits in familial Alzheimer's disease', *Brain*, vol. 133, no. 9, pp. 2702-2713.
<https://doi.org/10.1093/brain/awq148>

Digital Object Identifier (DOI):

[10.1093/brain/awq148](https://doi.org/10.1093/brain/awq148)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Brain

Publisher Rights Statement:

This is a pre-copy-editing, author-produced PDF of an article accepted for publication in *Brain* following peer review. The definitive publisher-authenticated version, Parra, M., Abrahams, S., Logie, R. H., Mendez, L. G., Lopera, F. & Della Sala, S. 1 (2010) "Visual short-term memory binding deficits in familial Alzheimer's disease", *Brain*. 133, 9, p. 2702-2713, is available online at: <http://brain.oxfordjournals.org/content/133/9/2702>

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Visual short-term memory binding deficits in familial Alzheimer's disease

Mario A. Parra^{1,2}
Sharon Abrahams¹
Robert H. Logie¹
Luis G. Méndez²
Francisco Lopera²
Sergio Della Sala¹

1 Human Cognitive Neuroscience, Centre for Cognitive Ageing and Cognitive Epidemiology, Psychology, University of Edinburgh, Edinburgh, UK

2 Neuroscience Group, University of Antioquia, SIU (Sede de Investigaciones Universitaria), 62 # 52-59, Antioquia, Medellín, Colombia

Correspondence to: Mario A. Parra, Psychology Department, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK E-mail: mprodri1@staffmail.ed.ac.uk

Summary Short-term memory binding is a memory function that underpins the temporary retention of complex objects (e.g. shapes with colours). In the verbal domain, this function has been found to be impaired in sporadic Alzheimer's disease. Whether short-term memory binding is also impaired in familial Alzheimer's disease, whether this impairment extends to the visual domain and whether it could be detected earlier than other cognitive deficits are issues yet to be investigated. Twenty two patients with familial Alzheimer's disease caused by the E280A single *presenilin-1* mutation, thirty carriers of the mutation who did not meet Alzheimer's disease criteria (asymptomatic carriers) and 30 healthy relatives (non-carrier healthy controls) were assessed with a visual short-term memory task and a neuropsychological battery. The short-term memory task assessed the recognition of shapes, colours or shape-colour bindings presented in two consecutive arrays (i.e. study and test). Changes, which always occurred in the test array, consisted of new features replacing studied features (single feature conditions) or of features swapping across items (the binding condition). The neuropsychological battery comprised tests of associative and non-associative memory, attention, language, visuospatial and executive functions. Patients with Alzheimer's disease and asymptomatic carriers performed significantly worse than healthy controls in the feature binding condition only. Group comparisons between asymptomatic carriers and healthy controls on standard neuropsychological tasks revealed no significant differences. Classification and area under the curve analyses confirmed that the binding task combines more sensitivity and specificity for patients with Alzheimer's disease and most notably for asymptomatic carriers of the mutation than other traditional neuropsychological measures. This suggests that visual short-term memory binding deficits may be a preclinical marker for familial Alzheimer's disease.

Keywords: Familial Alzheimer's disease, presenilin-1, short-term memory, memory binding, working memory, neuropsychological markers

Introduction

Memory binding is the function that supports the integration of the multiple elements of complex events within unified representations (von der Malsburg, 1999; Baddeley, 2000, 2007; Tulving, 2002; Zimmer *et al.*, 2006). In short-term memory binding underpins the temporary retention of associations or

conjunctions of features (e.g. shapes with colours) as integrated complex objects (Luck and Vogel, 1997; Treisman, 2006). In long-term memory, binding mediates the learning of associations between meaningful events (Baddeley, 2000; Tulving, 2002). Recent evidence suggests that retaining bindings in short-term memory and representing bindings as associations in long-term memory (i.e. learning) are functions supported by different memory processes (Colzato *et al.*, 2006; Treisman, 2006; Logie *et al.*, 2009), which are also differentially affected by brain damage and by cognitive ageing (Parra *et al.*, 2009a, b, 2010).

In daily living, binding on a temporary basis in short-term memory is essential to keep track of, for example, changing patterns of traffic while driving, or whether the white or the yellow pill has just been taken. Holding and updating these moment to moment changes in colour-shape binding in short-term memory is rather different from learning stable properties of the world such as face-name associations, or that the typical receptacle for mail in the UK is red and cylindrical. In the present article we focus on the little researched topic of short-term memory binding functions in Alzheimer's disease and examine its sensitivity and specificity for familial Alzheimer's disease.

We recently found that the process of binding information in verbal short-term memory is impaired in patients with sporadic Alzheimer's disease (Parra *et al.*, 2009a). This finding is complementary to the literature on associative learning and Alzheimer's disease, which suggests that forming associations between stimuli (e.g. paired associate learning) is impaired in sporadic and familial variants of the disease (Granholm and Butters, 1988; Buschke *et al.*, 1999; Ardila *et al.*, 2000; Swainson *et al.*, 2001; Fowler *et al.*, 2002; Lindeboom *et al.*, 2002; Lee *et al.*, 2003; Gallo *et al.*, 2004; Wang *et al.*, 2004; Lowndes and Savage, 2007; Lowndes *et al.*, 2008). It had been found that patients with Alzheimer's disease are unable to represent the association between objects and colours or pairs of words in verbal long-term memory (Buschke *et al.*, 1999; Della Sala *et al.*, 2000; Lloyd-Jones, 2005), or to represent in visual long-term memory the association between patterns and their spatial locations (Swainson *et al.*, 2001; O'Connell *et al.*, 2004).

However, a limitation in the use of associative learning in the assessment of Alzheimer's disease is that it also declines as part of normal ageing (de Jager *et al.*, 2002, 2005; Old and Naveh-Benjamin, 2008) and in chronic depression (Gainotti *et al.*, 1998; Fossati *et al.*, 2004; Kaschel *et al.*, 2009). This age-related long-term memory binding decline is significantly larger than the long-term memory decline observed for the individual elements that compose complex events (Old and Naveh-Benjamin, 2008). Therefore, paired associate learning is sensitive but not specific to Alzheimer's disease. The lack of specificity of associative learning deficits for Alzheimer's disease indicates that these tasks have limited potential in discriminating between the disease and the effects of normal ageing, and also have limited potential as prognostic indicators of who, among the elderly, will go on to develop the disease. Moreover, the usefulness of associative learning tasks to investigate memory functions in low-educated populations may encounter limitations (Uttl *et al.*, 2002) even if these tasks are adapted for language requirements (Ardila *et al.*, 1994). It is therefore necessary to investigate cognitive deficits that are both specific and sensitive to Alzheimer's disease, independent of any contribution of other factors such as age (MacPherson *et al.*, 2007) or sociocultural background. Short-term memory binding functions may therefore offer a promising approach.

In contrast to associative learning, binding of visual features in short-term memory is no more affected by age than is memory for individual features (Brockmole *et al.*, 2008; Parra *et al.*, 2009b). In Alzheimer's disease, binding deficits in short-term memory have been reported in the verbal domain (Parra *et al.*, 2009a). This deficit in Alzheimer's disease is in addition to, but greater than, impairments in short-term memory for individual features. Therefore, this pattern is different from that observed in healthy older

adults. However, it is still unknown whether these deficits extend across modality to visual short-term memory. Moreover, verbal short-term memory binding deficits were observed in patients diagnosed as suffering from late-onset sporadic Alzheimer's disease. It remains unknown whether they also characterize patients suffering from early-onset familial Alzheimer's disease. The latter presents a particularly important clinical group as they permit the investigation of cognitive impairment in individuals who have a genetic vulnerability to developing the disease. This has clear relevance for investigating which cognitive impairments may be more sensitive and specific to Alzheimer's disease in its early stages, or even preclinically (Ringman *et al.*, 2009).

If short-term memory binding deficits appear in the verbal and visual domain and are specific to both sporadic and familial Alzheimer's disease, they could be proposed as a signature of Alzheimer's disease. Moreover, short-term memory binding could be used to assess the development of Alzheimer's disease in a way that is unaccounted for by the effects of age.

Following these predictions, the present study investigated whether performance in a visual short-term memory binding task that has been shown to be insensitive to healthy ageing (Brockmole *et al.*, 2008) was impaired in patients with familial Alzheimer's disease and could also differentiate between carriers (who had not yet developed the disease) versus non-carriers of the mutation E280A in the *presenilin-1* gene (Lemere *et al.*, 1996). The presence of this mutation leads, in 100% of cases, to an autosomic dominant familial Alzheimer's disease which becomes clinically detectable at, on average, ~48 years of age (see Lopera *et al.*, 1997 for a clinical description of the disease). However, early cognitive deficits have been reported in carriers of this gene mutation at ~40 years of age (Lopera *et al.*, 1997), suggesting that the clinical expression of this disorder may start well before it fulfils classical criteria for the diagnosis of Alzheimer's disease. We hypothesized that if short-term memory binding deficits characterize Alzheimer's disease regardless of the clinical form, patients with E280A-related familial Alzheimer's disease should show impairment in this function. Moreover, based on previous literature on associative memory deficits in patients who later develop Alzheimer's disease (Swainson *et al.*, 2001; Fowler *et al.*, 2002), we predicted that visual short-term memory binding deficits may be observed in carriers, but not in non-carriers of the mutation who did not yet fulfil Alzheimer's disease criteria.

Materials and methods

Participant selection

The participants selected for the present study were recruited in a large kindred from the Colombian province of Antioquia, South America. Members of this kindred carry a gene mutation (i.e. E280A of *presenilin-1*) that leads to early-onset familial Alzheimer's disease in 100% of carriers (Lopera *et al.*, 1997). The recruitment protocol for all the participants consisted of three phases. The genetic screening, which was carried out using the methodology reported by the Alzheimer's Disease Collaborative Group (1995) (see also Lemere *et al.*, 1996; Lendon *et al.*, 1997), was aimed at confirming the presence of the mutation. Once the genotype was confirmed, the neurological and neuropsychological phases were performed. The results of these assessment phases allowed us to classify our research participants in three groups: (i) participants with early-onset familial Alzheimer's disease caused by the E280A single *presenilin-1* mutation (early-onset familial Alzheimer's disease carriers); (ii) carriers of the mutation who did not meet Alzheimer's disease criteria (asymptomatic carriers); and (iii) healthy individuals who were not carriers of the gene mutation and who were relatives of members of the other two groups (non-carrier healthy controls).

Twenty-two participants were early-onset familial Alzheimer's disease carriers, diagnosed according to the criteria established by the Diagnostic and Statistical Manual of Mental Disorders fourth

edition, text revision and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) group (McKhann *et al.*, 1984), and 30 were asymptomatic carriers who met neither Alzheimer's disease nor mild cognitive impairment criteria (Petersen, 2004) at the time of testing but who were positive for the E280A mutation. Additionally, we recruited a sample of 30 non-carrier healthy controls who were relatives of early-onset familial Alzheimer's disease carriers or asymptomatic carriers. The non-carrier healthy controls were negative for the E280A mutation and healthy according to the clinical interview and the results of the assessment phases described above. For both non-carrier healthy controls and asymptomatic carriers, additional inclusion criteria were: (i) negative history of neurological or psychiatric disorders; (ii) Mini-Mental State Examination score ≥ 24 ; and (iii) no memory complaints as documented by a self-report and a family questionnaire.

Early-onset familial Alzheimer's disease carriers, asymptomatic carriers and non-carrier healthy controls were matched according to the number of years spent in formal education (Table 1). Asymptomatic carriers and non-carrier healthy controls were additionally matched for the Mini-Mental State Examination scores. Asymptomatic carriers were significantly younger than early-onset familial Alzheimer's disease carriers and healthy controls. Further analysis with subgroups matched for age (including age above 35: $n = 17$ for each of asymptomatic carriers, early-onset familial Alzheimer's disease carriers and healthy controls) confirmed that age was not the factor accounting for the significant effects reported here (see Supplementary material). This is consistent with previous findings which demonstrate that age *per se* does not differentially affect this type of short-term memory binding processes (Brockmole *et al.*, 2008; Parra *et al.*, 2009b). All participants gave informed consent to take part in the study, which was approved by the relevant Ethics Committees.

Each participant underwent a colour vision assessment, followed by a binding perception condition. These conditions were undertaken to rule out the possibility that poor performance on the short-term memory binding task could result from visual or perceptual difficulties. Colour vision was initially assessed using the Dvorine pseudo-isochromatic plates (Dvorine, 1963). This test assesses colour vision within the red–green wavelengths. It is accepted that more than two errors suggest borderline or mild colour vision problems while five errors or more are indicative of colour vision deficits. In the present study, more than two errors were set as the exclusion criterion. Perception for shape-colour binding was then assessed with a task that simultaneously presented two arrays of coloured shapes, one in the upper half of the screen and one in the lower half. On each of 20 trials, participants searched for changes between the two arrays. The stimuli and design were the same as those described below for the shape-colour memory binding condition. The cut-off score, which indicates perceptual binding difficulties, was set at 90% correct (18 out of 20 trials). None of the participants recruited for the present study were excluded due to colour vision or perceptual binding problems. The demographic characteristics of the three groups of participants are shown in Table 1.

Assessment

The assessment consisted of two parts: a neuropsychological battery and a short-term memory task. The neuropsychological battery comprised the Mini-Mental State Examination (Folstein *et al.*, 1975), the Paired Associates Learning Task (Wechsler, 1945), Spanish versions of Verbal Fluency Tests (Letters-FAS, adapted from Sumerall *et al.*, 1997; and Animals), the Copy and Recall of the Complex Figure of Rey–Osterrieth (Osterrieth 1944; Rey, 1941), Part A of the Trail Making Test (Reitan, 1958) and the Wisconsin Card Sorting Test (Berg, 1948).

The short-term memory task was similar to that reported in Brockmole *et al.*'s Experiment 2 (2008). The task assessed visual short-term memory for arrays of stimuli presented on a computer screen. Stimuli were shapes (six-sided random polygons as shown in Fig. 1A), colours, or combinations of shapes and colours. Stimuli were randomly selected from a set of eight shapes and a set of eight colours and were

presented either independently (i.e. visual short-term memory for single features) or combined (i.e. visual short-term memory binding). Each type of stimulus was presented in a separate condition.

During the task, asymptomatic carriers and healthy controls were presented with arrays of three items while early-onset familial Alzheimer's disease carriers were presented with arrays of two items. Previous pilot studies suggested that these memory loads would allow performance levels in memory for single features to be equated across groups while keeping the early-onset familial Alzheimer's disease carriers' performance above floor and the controls' performance below ceiling. This follows our standard procedures (Logie *et al.*, 2004, 2007; Parra *et al.*, 2009a, b) for comparing the impact of experimental manipulations on patients and controls. In the present experiment, it ensures that any differences between groups on visual short-term memory binding performance can be attributed to the binding requirement and cannot be attributed to baseline differences in memory for single features.

The trial design for each condition of the visual short-term memory task is shown in Fig. 1B. The task was based on a change detection paradigm. At the beginning there was a fixation screen for 500 ms. This was followed by the study display which was presented for 2000 ms. The study display presented two or three items as explained above. The task for the participant was to remember these items. After the study display there was an unfilled retention interval of 900 ms which was followed by the test display. The participants were asked to recognize if the items presented in the test display were the same or different from those presented at study. In 50% of the trials, the items were the same in both displays (i.e. 'same trials'). In the other 50%, two items in the test display were different (i.e. 'different trials').

Two conditions assessed visual short-term memory for single features and one assessed the binding of these features in visual short-term memory. In the 'shape only' and 'colour only' conditions, arrays of shapes (Fig. 1A) or colours were presented in the study display. In the test display for the 'different trials', two new shapes or new colours from the study array were replaced with two new shapes or two new colours. Hence, in these conditions, only visual short-term memory for individual features was required to detect a change. In the shape-colour binding condition, combinations of shapes and colours were presented in the study display. In the test display for the 'different trials', two shapes swapped the colours in which they had been shown in the study display. Hence, memory for bindings of shape and colour in the study display was required in order to detect this change. No shape or colour was repeated within a given array. Each condition consisted of 15 practice trials followed by 32 test trials. Out of 32, 16 were 'same trials' (the study and test displays presented identical items) and 16 were 'different trials' (Fig. 1B). The task for the participants was to detect when a change had occurred and to respond orally 'same' or 'different' as appropriate. The experimenter entered participants' responses using the keyboard. Trials were fully randomized across participants and conditions were delivered in a counterbalanced order.

Statistical analysis

The scores on the neuropsychological battery were compared across groups using one-way ANOVA followed by Bonferroni-corrected *post hoc* tests (Table 1). For the visual short-term memory task, performance of early-onset familial Alzheimer's disease carriers with two items and of healthy controls and asymptomatic carriers with three items were compared using a two-way mixed ANOVA model. This manipulation was aimed at equating performance across groups in conditions assessing short-term memory for single features. Hence, it permitted the investigation of whether visual short-term memory binding deficits are specific to early-onset familial Alzheimer's disease and cannot be explained by the task demands of remembering individual features. The between-subjects factor was group (healthy controls versus asymptomatic carriers versus early-onset familial Alzheimer's disease carriers) and the within-subjects factor was condition (shape only versus colour only versus shape-colour binding). *Post hoc* comparisons were carried out across groups for each condition separately ($3 \times 3 = 9$ contrasts) and across

conditions for each group separately ($3 \times 3 = 9$ contrasts). With a total of 18 pairwise comparisons, the Bonferroni corrected alpha level was set at 0.003. For the main effects in the short-term memory task, the effects size (η) and power (Pw) were calculated (Cohen, 1988). The effect size was defined as the square root of the proportion of the total variance attributed to an effect [$\eta = \text{Sqrt}(\text{Eta})$] (Leech *et al.*, 2007). According to Cohen's (1988) criteria, $\text{Sqrt}(\text{Eta})$ values >0.24 represent medium effect sizes and >0.31 represent large effect sizes. Two dependent variables were calculated: percentage of correct recognition and sensitivity for change detection (Stanislaw and Todorov, 1999). The percentage of correct recognition was defined as the proportion of trials correctly performed (i.e. hits for different trials and correct rejections for same trials) out of 32 per condition, expressed as a percentage. Additionally, we implemented the calculation of the Signal Detection Theory (Stanislaw and Todorov, 1999). We chose A' (Pollack and Norman, 1964) as the sensitivity measure, since this has been suggested to be a valid measure of performance in change detection tasks as it does not have indeterminacy when a participant does not make false alarms. The information provided by A' is complementary to that obtained from the Percentage of correct recognition as it provides information on the ability to extract the signal (i.e. changing items) from the noise (i.e. distractors). Therefore, if poor performance (i.e. low Percentage of correct recognition) is accounted for by low A' (sensitivity), this would suggest that the memory impairment is due to difficulties in keeping separate in memory the signal from the noise (see Xu, 2002 for the formula used).

The percentage of correct recognition was chosen to perform further classification analysis. This was aimed at investigating the accuracy of the neuropsychological and visual short-term memory variables to detect impaired performance at an individual level. To this aim, standard neuropsychological scores (mean ± 2 SD) obtained from the same or similar Spanish speaking populations (Ardila *et al.*, 1994) were used as cut-off. In the case of the short-term memory tasks, the standard values were obtained from the controls recruited for the present study. In order to control for outliers in the healthy controls group we performed a test for outlier detection (Barnett *et al.*, 1994; see Supplementary material for the results of this analysis). The number of participants that performed below the cut-off was determined. Contingency tables were then constructed to compare, using chi-square analysis, the proportion of participants that were classified as below or above cut-off within each group for each dependent variable. Finally, area under the curve analysis was performed to investigate the sensitivity and specificity of the neuropsychological and short-term memory variables to classify the participants correctly. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

Results

Neuropsychological assessment

The results of the neuropsychological assessment are presented in Table 1. Comparisons carried out across groups revealed that early-onset familial Alzheimer's disease carriers had poorer memory performance than both healthy controls and asymptomatic carriers in the Paired Associates Learning task (Wechsler, 1945) and in the Recall of the Rey–Osterrieth Complex Figure (Rey, 1941; Osterrieth, 1944). Executive and attention functions were also significantly worse in early-onset familial Alzheimer's disease carriers than in healthy controls and asymptomatic carriers as assessed by the Verbal Fluency Tests (Letters-FAS and Animals), the Wisconsin Card Sorting Test (Berg, 1948) and the Trail Making Test (Reitan, 1958). These neuropsychological findings suggest that early-onset familial Alzheimer's disease carriers presented with an amnesic and dysexecutive syndrome resembling the behavioural pattern described for sporadic Alzheimer's disease (Greene *et al.*, 1995). Finally, mean performance of healthy controls and asymptomatic carriers did not significantly differ on any of the neuropsychological test scores.

Short-term memory task

ANOVA with percentage of correct recognition

Significant main effects were found for Group [$F(2,79) = 7.6$, $P = 0.001$; $\gamma = 0.40$, $P_w = 94$], Condition [$F(2,158) = 282.9$, $P < 0.001$; $\gamma = 0.88$, $P_w = 100$] and for the interaction of Group \times Condition [$F(4,158) = 14.86$, $P < 0.001$; $\gamma = 0.52$, $P_w = 100$] (Fig. 2A).

Post hoc comparisons following the significant interaction showed that early-onset familial Alzheimer's disease carriers, asymptomatic carriers and healthy controls did not differ significantly in memory performance on the shape only or colour only conditions. Early-onset familial Alzheimer's disease carriers performed significantly more poorly than healthy controls (but not than asymptomatic carriers) in the condition assessing memory for shape-colour binding [mean difference (MD) = 18.04, standard error (SE) = 2.97, $P < 0.001$]. Asymptomatic carriers also performed more poorly than healthy controls in the condition assessing memory for shape-colour binding (MD = 12.63, SE = 2.73, $P < 0.001$).

The analysis across conditions showed that for both early-onset familial Alzheimer's disease carriers and asymptomatic carriers, performance was in the following format: memory for shape-colour binding < memory for shape only < memory for colour only (all the comparisons were significant at $P < 0.001$). For the healthy controls, performance was in the form of: (memory for shape-colour binding = memory for shape only) < memory for colour only. These results suggest that when shape-colour bindings were to be retained in visual short-term memory, early-onset familial Alzheimer's disease carriers and asymptomatic carriers performed alike and both were significantly worse than healthy controls' scores.

ANOVA with A' data

A significant main effect was found for Group [$F(2,79) = 11.34$, $P < 0.001$; $\gamma = 0.47$, $P_w = 99$]. The assumption of homogeneity of variance and covariance was violated for the factor condition [Mauchly's $W(2) = 0.56$, $P < 0.001$]. Hence, we corrected the degrees of freedom using the Greenhouse–Geisser epsilon (0.694). After applying this correction factor, significant main effects were also found for Condition [$F(1.38, 109.65) = 147.34$, $P < 0.001$; $\gamma = 0.81$, $P_w = 100$] and for the interaction of Group by Condition [$F(2.77, 109.65) = 17.12$, $P < 0.001$; $\gamma = 0.55$, $P_w = 100$] (Fig. 2B).

Post hoc comparisons carried out across groups showed that early-onset familial Alzheimer's disease carriers, asymptomatic carriers and healthy controls did not show significant differences in sensitivity in any of the contrasts performed in the conditions assessing memory for shape only or colour only. Early-onset familial Alzheimer's disease carriers proved to be significantly less sensitive than healthy controls to detect changes in the condition assessing memory for shape-colour binding (MD = 0.22, SE = 0.04, $P < 0.001$). No other contrast performed across groups in the condition assessing memory for shape-colour binding resulted in significant effects.

The analysis across conditions showed that the pattern of sensitivity in early-onset familial Alzheimer's disease carriers and asymptomatic carriers was in the following format: memory for shape-colour binding < shape only < memory for colour only (all the comparisons were significant at $P < 0.001$ except for the contrast between shape and colour only in patients with early-onset familial Alzheimer's disease in which $P = 0.003$). For healthy controls the pattern of sensitivity was in the form of (memory for shape-colour binding = memory for shape only) < memory for colour only.

Classification analysis

Classification analysis was carried out to investigate whether the group effects described above were representative of performance of each individual within the three groups. Table 2 shows the results of this analysis. When the number of asymptomatic carriers and healthy controls performing below cut-off in the neuropsychological tasks was entered into contingency tables analyses, the proportion of participants that performed below cut-off was small and did not significantly differ across groups (except for the Recall of the Rey Figure in which more asymptomatic carriers performed below cut-off). A significantly larger proportion of early-onset familial Alzheimer's disease carriers performed below cut-off in almost all the neuropsychological tasks as compared to asymptomatic carriers and healthy controls. The Copy of the Rey Figure was the only task in which the proportion of asymptomatic carriers and early-onset familial Alzheimer's disease carriers performing below cut-off was not significantly different.

The analysis of the visual short-term memory variables revealed that the proportion of asymptomatic carriers and early-onset familial Alzheimer's disease carriers performing below cut-off in the condition assessing shape-colour binding was significantly larger than the proportion of healthy controls (none of the participants from this last group fulfilled outlier criteria, see Supplementary material). The proportions for the first two groups did not differ significantly. No other contrast performed with this task resulted in significant effects. These results suggest that the group effects described above are representative of performance of a large proportion of participants within each group of carriers of the E280A mutation and support the usefulness of the short-term memory task presented here in detecting significant deficits on an individual level. This may have important implications for the use of this task within clinical settings.

Finally, performance on the Paired Associates Learning task, Recall of the Rey–Osterrieth Complex Figure and the shape-colour binding condition were chosen for area under the curve analysis as these were the tasks in which the most asymptomatic carriers and early-onset familial Alzheimer's disease carriers were found to be impaired (Table 2). Figure 3A–C shows the results of the analysis. The task assessing short-term memory for shape-colour binding proved to be sensitive for detecting both early-onset familial Alzheimer's disease carriers (sensitivity = 77%, PPV = 77%, NPV = 83%) and asymptomatic carriers (sensitivity = 73%, PPV = 81%, NPV = 76%) and for separating them from healthy controls (specificity = 83%). The Paired Associates Learning task proved sensitive for detecting patients with early-onset familial Alzheimer's disease (sensitivity = 82%, PPV = 72%, NPV = 85%) but much less so for detecting asymptomatic carriers (sensitivity = 40%, PPV = 63%, NPV = 56%). This task was also a little less specific than the short-term memory binding task (specificity = 77%). In the case for the Recall of the Rey–Osterrieth Complex Figure, this task proved insensitive to detect asymptomatic carriers (sensitivity = 23.3%, PPV = 86%, NPV = 55%) but more sensitive to detect early-onset familial Alzheimer's disease carriers (sensitivity = 77%, PPV = 94%, NPV = 85%). This task however, showed high specificity (96%).

Discussion

The results showed a clear impairment in visual short-term memory binding in both early-onset familial Alzheimer's disease carriers and asymptomatic carriers of the mutation. These results cannot be accounted for by differences between groups in general memory capacity, since memory performance on the single feature conditions was equated across the three groups. Logie *et al.* (2004, 2007) and Parra *et al.* (2009a) used a similar methodology for comparing the impact of experimental manipulations on patients and controls. For example, Logie *et al.* (2004, 2007) asked their participants to perform two concurrent tasks each titrated to the individuals (i.e. by using their own span). Thereby any cost found during the concurrent condition could not be attributed to the demands of each task. Parra *et al.* (2009a) were able to

compare performance of patients with Alzheimer's disease and controls by altering the number of to be remembered items in the baseline (single feature) condition to equate performance between groups. In the current study this methodology enabled the investigation of binding functions in visual short-term memory once baseline differences due to memory for single features were controlled. This technique also avoided floor effects in the patient groups and ceiling effects in the controls.

Healthy controls performed the memory binding condition as well as they performed the condition assessing memory for shapes only, indicating that memory binding was not more demanding than the shape only condition. Furthermore, this suggests that healthy individuals can represent in visual short-term memory the shapes and colours used in this task as integrated units (Luck and Vogel 1997; Wheeler and Treisman 2002; Brockmole *et al.*, 2008). Therefore, the results presented here suggest a differential and specific impairment in visual short-term memory binding in early-onset familial Alzheimer's disease carriers and asymptomatic carriers of this mutation who have not yet developed the disease. This impairment is characterized by a loss of the ability to represent objects integrated as a whole in visual short-term memory.

Additionally, the results from the current study, in which the visual recognition of features was assessed, together with those from previous studies using free recall of verbal features (Parra *et al.*, 2009a), suggest that short-term memory binding deficits in Alzheimer's disease do not seem to be restricted to specific types of information (visual and verbal stimuli) or to a specific retrieval process (recall and recognition).

Asymptomatic carriers remembered shapes only or colours only no differently from the healthy controls. However, they could not remember the temporary binding between these features to the same extent as the controls. The analyses across conditions showed that early-onset familial Alzheimer's disease carriers and asymptomatic carriers performed similarly with poorer performance on memory for binding than in both memory for single feature conditions. This contrasted with controls' performance in which memory for binding and memory for shape did not differ. For early-onset familial Alzheimer's disease carriers (but not for asymptomatic carriers), low sensitivity for change detection (A') accounted for poor memory performance. This suggests that as the disease progresses, the mechanisms underpinning memory deterioration also change. Even though asymptomatic carriers were able to keep separate in short-term memory the signal from the noise during recognition of changes, they were less able to retain information from the signal only in the condition where different pieces of information had to be bound together (i.e. shape-colour binding).

It is striking that, despite the impairment in visual short-term memory binding shown by asymptomatic carriers, group comparisons revealed that asymptomatic carriers and healthy controls did not differ significantly in scores on any of the standard neuropsychological tasks and both were significantly different from early-onset familial Alzheimer's disease carriers in tasks assessing general memory, executive and attention functions. Classification analysis showed that more asymptomatic carriers were impaired than healthy controls on only one standard memory measure, Recall of the Rey Figure. However, as the classification analysis showed, this test did not combine sensitivity with specificity for asymptomatic carriers. The classification analyses also confirmed that the results obtained with group comparisons were accounted for by performance of the majority of the participants recruited within each group.

Of note, the Paired Associates Learning task and the shape-colour binding were the two tasks in which the most asymptomatic carriers and early-onset familial Alzheimer's disease carriers performed below cut-off. This is in keeping with the literature on associative memory and Alzheimer's disease which suggests that in the course of the disease, these forms of memory seem to deteriorate earlier and deficits are more pronounced than for non-associative memory (Granholm and Butters 1988; Buschke *et al.*, 1999; Swainson *et al.*, 2001; Fowler *et al.*, 2002; Lindeboom *et al.*, 2002; Lee *et al.*, 2003; Gallo *et al.*, 2004; Lowndes and Savage 2007; Lowndes *et al.*, 2008). For example, in the study by Fowler *et al.* (2002), the authors assessed a group of individuals at risk for developing sporadic Alzheimer's disease (i.e.

patients with mild cognitive impairment) with the Cambridge Neuropsychological Test Automated Battery Paired Associates Learning test. They found that those who performed poorly on this test at baseline were more likely to convert to Alzheimer's disease in 24 months of follow-up (see also Swainson *et al.*, 2001; O'Connell *et al.*, 2004). However, the actual contribution of the Paired Associates Learning test to determine who, among the elderly, can deviate from the course of normal ageing and go on to develop Alzheimer's disease remains unclear because this test is sensitive to the effects of age (see de Jager *et al.*, 2002, 2005). This is not the case for the short-term memory binding task presented here which has proved insensitive to the effects of normal ageing (Brockmole *et al.*, 2008; see Supplementary material for further analysis with age of the current data). If we were to assume that the asymptomatic carriers assessed here are at an equivalent point in the course of the disease as individuals with pre-mild cognitive impairment progressing to sporadic Alzheimer's disease, we would propose that the short-term memory binding task may be useful for detecting cognitive changes in this at risk population. In fact, Lopera *et al.* (1997) described that E280A-related Alzheimer's disease resembles phenotypically sporadic Alzheimer's disease in almost all its features. However, the results from other studies suggest that there may be phenotypic differences across genetic and sporadic Alzheimer's disease (Holmes, 2002; Mosconi *et al.*, 2003). Even mutations of the same gene (i.e. *presenilin-1*) may lead to different phenotypes. Ringman *et al.* (2005) assessed a sample of young carriers (average age 28.9) of the mutation A431E of the *presenilin-1* gene, which leads to early-onset familial Alzheimer's disease. They showed significant neuropsychological impairments. The carriers of the mutation E280A of the *presenilin-1* gene assessed in the present study were, as a group, older than those assessed by Ringman *et al.* (2005). However, they were asymptomatic. Therefore, the extent to which findings in genetic Alzheimer's disease could be used to predict changes in sporadic Alzheimer's disease and vice versa, still requires more investigation.

The relationship between neuroanatomical damage in Alzheimer's disease and associative learning deficits has been well established. There is a great deal of evidence supporting the role of the hippocampus in associative learning (Mayes *et al.*, 2007). The high sensitivity of the Paired Associates Learning task to Alzheimer's disease has been linked to early damage to the hippocampus (Mayes *et al.*, 2007; Lowndes *et al.*, 2008). Short-term memory binding also implies association. However, there is evidence suggesting that inter-item associations (i.e. items-locations as in the Paired Associates Learning task) and intra-item associations (i.e. shapes-colours as in the current short-term memory binding task) are functions supported by different brain regions (Piekema *et al.*, 2006, see also Mayes *et al.*, 2004 for the case YR). The fact that the visual short-term memory binding task presented here has proved insensitive to the effects of age can be explained by these earlier observations. As shape-colour binding does not require the hippocampus, this test may be less sensitive to normal ageing, as older adults show some degree of hippocampal atrophy (Grady *et al.*, 2003; Grady 2008). However, shape-colour binding does require effective brain connectivity (Zimmer *et al.*, 2006). The Alzheimer's disease pathology is characterized by a predominant disconnection. It might be possible that, using appropriate tests, this disconnecting process could be detected earlier than other structural damage resulting from neural death (i.e. hippocampal atrophy). This proposal may suit recent reports (Bates, 2009) which suggest that future cognitive markers for Alzheimer's disease should detect the diseases in stages before substantial neuronal cell loss has occurred.

In the present study we found that the Paired Associates Learning task (Wechsler, 1945) was the neuropsychological task in which the largest number of healthy controls performed below cut-off. This may have negative implications for the use of verbal associative learning tasks to investigate low educated populations (Ardila *et al.*, 1994). The observation that fewer healthy controls performed below cut-off in the short-term memory task supports the usefulness of tests with low verbal demands to assess such populations. Other tasks that have proved sensitive for detecting cognitive changes in patients with mild cognitive impairment are the visual delayed matching-to-sample task (Barbeau *et al.*, 2004) and The

Montreal Cognitive Assessment (Nasreddine *et al.*, 2005). The Montreal Cognitive Assessment yielded sensitivity of 90 and 100% for mild cognitive impairment and Alzheimer's disease, respectively, while its specificity was 87%. These tasks may however be performed poorly by low-educated population as they pose high-semantic demands. A further limitation of the current tests used to detect Alzheimer's disease is that they are also performed poorly by some healthy older adults. The format of the Montreal Cognitive Assessment is similar to that of the Mini-Mental State Examination. Ardila *et al.* (1994) suggested 23 points as the appropriate Mini-Mental State Examination cut-off score for subjects with minimal education. This suggests that even if these tasks were standardized in this population, their outcomes would be influenced by this sociodemographic factor. The task presented here has the advantage that its outcomes are unaccounted for by the effects of age (Brockmole *et al.*, 2008) or low sociocultural background.

Both the Paired Associates Learning task and the short-term memory task showed high sensitivity and specificity at detecting early-onset familial Alzheimer's disease carriers. However, the short-term memory binding task investigated here was much more sensitive than was the Paired Associates Learning at detecting asymptomatic carriers who had not yet developed the disease. Even though the Recall of the Rey–Osterrieth Complex Figure proved specific, its sensitivity for both asymptomatic carriers and early-onset familial Alzheimer's disease carriers was very low. This suggests that in the course of developing E280A-related familial Alzheimer's disease, visual short-term memory binding deficits can be detected much earlier than impairments of other functions, including associative learning, which are assessed by traditional neuropsychological tasks. Ringman *et al.* (2009) suggest that the study of familial Alzheimer's disease provides an opportunity to test various criteria for early Alzheimer's disease. The results of the present study support this statement and suggest that short-term memory binding functions may form part of the assessment criteria for early Alzheimer's disease.

In summary, we have found that visual short-term memory binding is affected in E280A-related familial Alzheimer's disease. Notably impairments of this function were also observed in carriers of the mutation who were asymptomatic on standard neuropsychological tests. These results suggest that short-term memory binding deficits are a fundamental feature of Alzheimer's disease and may be a pre-clinical marker for early-onset E280A familial Alzheimer's disease in carriers of the mutation. It is also possible that the short-term memory binding deficit reflects the presence of the gene mutation/phenotype and that this gene mutation also leads in 100% of cases to conversion to Alzheimer's disease in early middle age. However, since similar short-term memory binding deficits have also been found in late-onset sporadic Alzheimer's disease these results raise the question as to whether these deficits might also prove to be a preclinical marker for all forms of the disease. Future studies should investigate this hypothesis with short-term memory binding tasks that have proved insensitive to the effects of normal ageing, highly sensitive to the effects of Alzheimer's disease and are able to detect the development of genetic variant of the disease much earlier than other traditional cognitive procedures.

Footnotes

Abbreviations:

NPV: negative predictive value

PPV: positive predictive value

Funding

This study was supported by the Programme Alban, the European Union Programme of High Level Scholarships for Latin America, scholarship No. E04D048179CO awarded to Mario A. Parra (Alban supervisor: S.D.S.). M.A.P.'s work is currently supported by a grant from the Neuroscience Program call

of 'The San Paolo Foundation'. The study is also sponsored by Colciencias, Grants 1115-408-20512 and 1115-343-19127 awarded to the Neuroscience Group, University of Antioquia, Colombia in collaboration with the M.A.P. and S.D.S. The project was also partially supported by ALFA Eurocaribbean Neurosciences Network, contract AML/B7-311/97/0666/II-0322-FA-FCD-FI-FC, in which S.D.S. and F.L. were partners, and was set in the context of The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the UK cross council Lifelong Health and Wellbeing Initiative grant number G0700704/84698.

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Tables and Figures

Table 1. Demographic and neuropsychological data for the three groups of participants

	Healthy controls (<i>n</i> = 30)		Asymptomatic carriers (<i>n</i> = 30)		E-FAD carriers (<i>n</i> = 22)		One-way ANOVA			
							<i>F(P)</i>	<i>Post hoc tests (P-value)</i>		
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range		Asymptomatic Carriers versus Healthy Controls	Asymptomatic Carriers versus E-FAD	Healthy controls versus E-FAD
Age ^{a,b}	40.9 (9.3)	(24–58)	35.6 (6.6)	(23–46)	45.2 (4.8)	(32–52)	11.2 (0.000)	0.018	0.001	0.12
Years of education	9.5 (3.2)	(4–16)	9.3 (4.4)	(1–20)	8.5 (4.2)	(1–18)	0.5 (0.60)	1	1	0.98
Mini-Mental State Examination ^{b,c}	29.4 (1.3)	(24–30)	29.2 (1.3)	(25–30)	25.5 (3.7)	(18–30)	23.76 (0.000)	1	0	0
Paired Associates Learning ^{b,c}	13.1 (3.5)	(6–19)	12.1 (4.0)	(5–20)	7.4 (3.5)	(3–16)	15.84 (0.000)	1	0	0
Verbal Fluency (Letters-FAS) ^{b,c}	12.4 (3.6)	(6–19)	11.5 (5.8)	(2–29)	8.4 (3.6)	(3–16)	5.217 (0.007)	1	0.04	0.007
Verbal Fluency (Animals) ^{b,c}	20.5 (4.1)	(12–28)	18.6 (5.3)	(9–32)	14.1 (3.6)	(9–21)	13.27 (0.000)	0.33	0.002	0
REY-Copypc	27.5 (4.7)	(19–34)	24.2 (7.0)	(4–34)	21.1 (7.8)	(3–31)	6.11 (0.003)	0.15	0.32	0.003
REY-Recall ^{b,c}	16.3 (6.1)	(4–26)	13.2 (6.6)	(3–26)	4.0 (4.3)	(0–19)	28.85 (0.000)	0.17	0	0
Trail Making Test ^{b,c}	61.7 (26.5)	(17–138)	73.7 (52.2)	(31–290)	114.76 (61.08)	(39–275)	9.66 (0.000)	1	0.004	0
Wisconsin Card Sorting Test Categories ^{b,c}	3.5 (1.5)	(1–6)	3.3 (1.5)	(0–6)	1.6 (1.0)	(0–3)	13.29 (0.000)	1	0	0
Wisconsin Card Sorting Test Concept ^{b,c}	11.7 (7.0)	(6–31)	11.4 (7.4)	(2–37)	21.7 (17.5)	(6–46)	6.91 (0.002)	1	0.004	0.005

a Asymptomatic carriers versus non-carrier healthy controls different at $P < 0.05$.

b Asymptomatic carriers versus early-onset familial Alzheimer's disease carriers different at $P < 0.05$

c Non-carrier healthy controls versus early-onset familial Alzheimer's disease carriers different at $P < 0.05$.

E-FAD = early-onset familial Alzheimer's disease carriers.

Figure 1. (A) Shapes used to construct stimuli arrays. (B) Experimental conditions and trial designs.

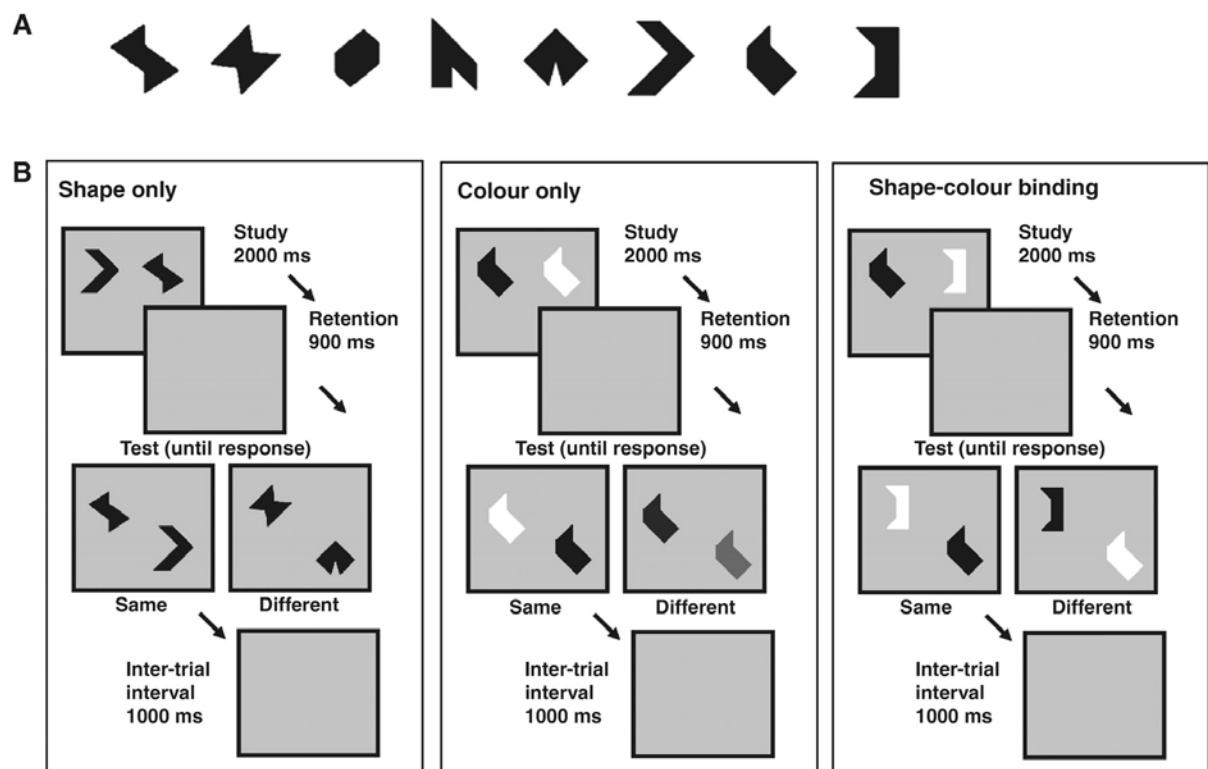


Figure 2. (A) Percentage of correct recognition and (B) sensitivity (A') in non-carrier healthy controls, asymptomatic carriers and early-onset familial Alzheimer's disease carriers (E-FAD) in the short-term memory task (error bars represent the standard errors of the mean).

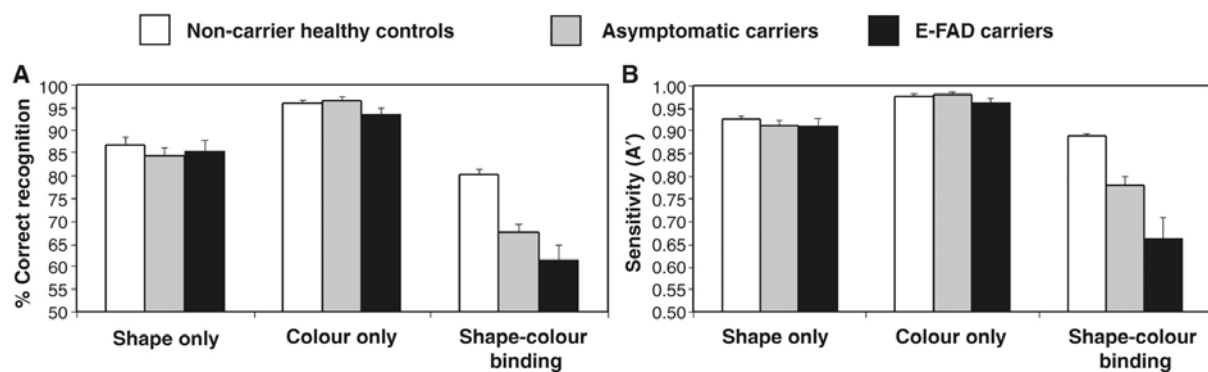


Table 2. Results of the classification analysis carried out for each variable at individual level

Cut-off score	Number performing below cut-off		Chi-square analysis χ^2 (P)				Healthy controls versus E-FAD
		Healthy controls (out of 30)	Asymptomatic carriers (out of 30)	E-FAD carriers (out of 22)	Asymptomatic carriers versus healthy controls	Asymptomatic carriers versus E-FAD	
Shape only ^a	78	3	7	5	1.92 (0.17)	0.002 (0.99)	1.58 (0.21)
Colour only ^a	90.9	3	2	5	0.218 (0.64)	2.81 (0.09)	1.58 (0.21)
Shape-colour binding ^a	73.6	5	22	17	19.5 (0.00)	0.105 (0.75)	19.1 (0.00)
Mini-Mental State Examination ^b	28.7	3	4	16	0.162 (0.69)	18.9 (0.00)	21.5 (0.00)
Paired Associates Learning ^c	11	7	12	18	1.93 (0.17)	9.09 (0.00)	17.4 (0.00)
Verbal Fluency (Letters-FAS) ^b	7	1	4	9	1.96 (0.16)	5.15 (0.02)	11.5 (0.00)
Verbal Fluency (Animals) ^b	14.4	2	6	13	2.31 (0.13)	8.36 (0.00)	4.14 (0.04)
REY-Copy ^b	19	1	5	8	2.96 (0.08)	2.63 (0.11)	9.68 (0.00)
REY-Recall ^b	6	1	6	17	4.04 (0.04)	16.9 (0.00)	30.7 (0.00)
Trail Making Test ^b	114	2	4	8	0.741 (0.40)	3.79 (0.05)	7.21 (0.01)
Wisconsin Card Sorting Test Categories ^b	2	2	2	11	0 (1)	12.7 (0.00)	12.7 (0.00)
Wisconsin Card Sorting Test Concept ^b	21	3	4	9	0.162 (0.69)	5.15 (0.02)	6.83 (0.01)

E-FAD = early-onset familial Alzheimer's disease carriers. $X^2(P)$ = chi-square and associated P -value

^a The cut-off scores were obtained from non-carrier healthy controls.

^b The cut-off scores correspond to the norms ($M \pm 2$ SD) obtained from the same population.

^c The cut-off score corresponds to the norms ($M \pm 2$ SD) obtained from a Spanish speaking population (Ardila *et al.*, 1994).

Figure 3. Area under the curve analysis with asymptomatic carriers' and early-onset familial Alzheimer's disease carriers' (E-FAD) performance on the (A) shape-colour binding condition of the visual short-term memory task, on the (B) Paired Associates Learning (PAL) task from the Wechsler Memory Scale, and on the (C) Recall of the Rey–Osterrieth Complex Figure.

